Postgraduate Medical Journal (December 1972) **48**, 714–721.

Classification of the secondary cardiomyopathies

The pathologist's view

ARIELA POMERANCE

SECONDARY cardiomyopathy is defined as heart muscle disease of known cause or association. Naming particular diseases is preferable where individual conditions are being referred to e.g. myocardial sarcoid, cardiac amyloidosis, scleroderma heart disease, since the term cardiomyopathy without qualification is generally accepted as referring to the primary forms. Nevertheless, a convenient collective term is needed to cover all the conditions which have to be excluded before a diagnosis of primary cardiomyopathy can be made. There are a very large number of such conditions and Hudson (1970) lists over 100. Faced with an exercise in classification of this magnitude most pathologists would first divide the conditions according to anatomical pathology, then consider the types of pathological reaction and finally the aetiology (Table 1).

The material seen by the pathologist ranges from a single stained slide to the complete body for necropsy, with full clinical data. The first step is to exclude vascular or valvular conditions which may be responsible for the heart muscle disease. Of the vascular lesions, coronary atheroma is the commonest known cause of heart muscle disease, so much so, that ischaemic heart disease is not usually regarded as a secondary cardiomyopathy. Rarer causes of coronary occlusion such as vasculitis with thrombosis, or fibrosis following trauma (including cardiac surgery) should also be kept in mind. Valvular incompetence secondary to aortic wall disease may be due to cystic medionecrosis either as in the Marfan syndrome and similar uncommon genetically determined connective tissue disorders or more often as an isolated finding. It may also occur due to inflammatory changes as in ankylosing spondylitis and syphilis. Primary valve disease causing myocardial changes is mainly fibrotic as in rheumatic-type valve disease, or calcific as in isolated aortic stenosis. Less common underlying pathologies are perforation of valve cusps following infective

TABLE 1. Pathology of secondary cardiomyopathies

Microscopic pathology		Causes
Vessels		
Coronary	Atherosclerosis	
Aorta	Medionecrosis	Generalized or localized connective tissue defect
	Inflammation	Ankylosing spondylitis.
		Syphilis
Valves	Fibrosis	Valvulitis (rheumatic and other)
	Calcification	Degenerative or past inflammation
	Mucoid degeneration	Genetic or isolated
Myocardium	Inflammation:	
	active, chronic granulomatous with collagen changes	See Table 2
	Fibrosis	Post-inflammatory
		Genetic ataxias and dystrophies
		Mucoviscidosis
		Collagen diseases
		Post-surgery
	Depositions:	
	in muscle fibres	Glycogen storage disease; haemochromatosis; calcification
	between muscle fibres	Mucopolysaccharidoses; oxalosis; myxoedema; amyloidosis
	Small vessel changes	
	embolic	Bacterial and non-bacterial endocarditis
	inflammatory	Collagen diseases
	Non-specific changes or no apparent abnormality	Nutritional
		Toxic
		Endocrine diseases
		Vascular shunts
		Chronic lung disease

endocarditis, mucoid degeneration producing 'floppy' mitral or aortic cusps, and, very rarely, storage diseases such as mucopolysaccharidoses and hypercholesterolaemia.

Having excluded vascular and valvular causes of heart muscle disease we come to conditions directly involving the myocardium. Microscopy may show inflammatory changes of various types, fibrosis, abnormal depositions or abnormalities of small vessels, but in many conditions the histological changes appear minor and non-specific or no abnormality may be apparent on ordinary light microscopy.

Inflammatory myocardial disease (Table 2)

An infective aetiology is suggested by the presence of large numbers of inflammatory cells with relatively little myocardial necrosis (Fig. 1).

TABLE 2. Conditions associated with inflammatory myocardial disease

Infections	
Virus	Coxsackie, mumps, influenza, psittacosis
Rickettsial	Q fever
Bacterial	Diphtheria, brucella, tubercle
Spirochaetal	Leptospira, syphilis
Fungal	Histoplasma, candida
Protozoal	Toxoplasma, trypanosoma
Helminthic	Cysticercus, echinococcus
Granulomatous	Sarcoid
	Giant cell myocarditis
'Collagen' diseases	Rheumatic
	Rheumatoid
	Scleroderma

In the later stages only scanty small aggregates of inflammatory cells are present. These are mainly mononuclear, usually including a few plasma cells, and there is an increase in interstitial connective tissue (Fig. 2).

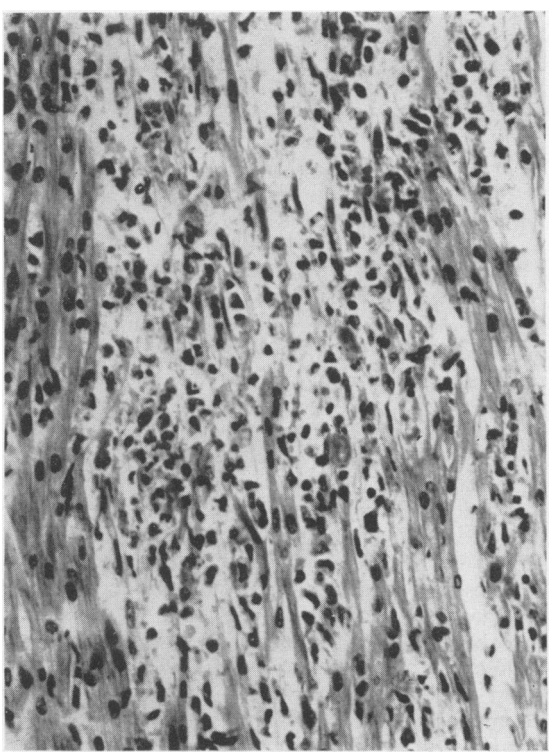

FIG. 1. Acute myocarditis. Focal myocardial necrosis is present but the picture is dominated by the dense pleomorphic inflammatory cell infiltrate. From a baby dying of Coxsackie myocarditis. H & E, × 290.

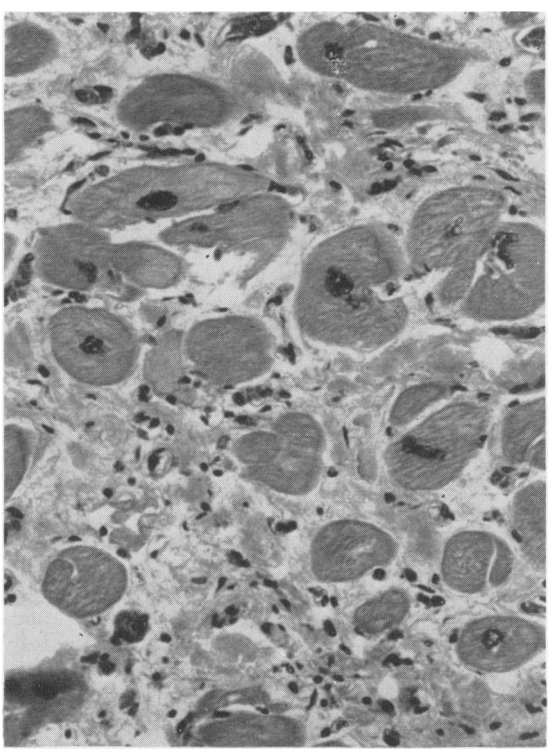

FIG. 2. Chronic myocarditis. Scanty chronic inflammatory cell foci, including plasma cells, with early fibrosis between myofibres. From a child with 4 weeks' general malaise following a febrile episode, who died of congestive cardiac failure. H & E, × 320.

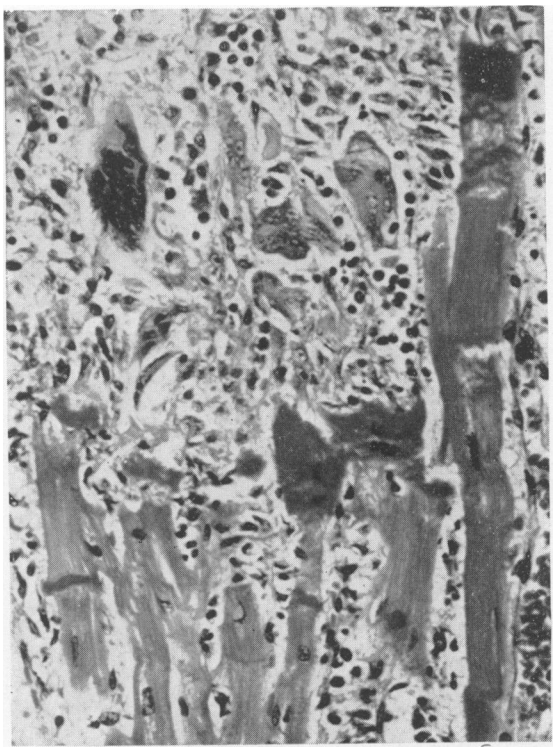

FIG. 3. Giant cell myocarditis. The myogenic origin of the giant cells is clearly seen. H & E, × 320.

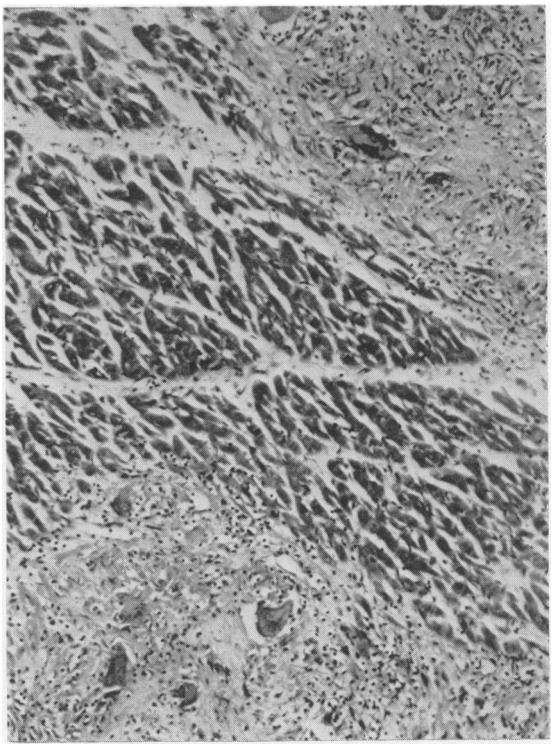

FIG. 4. Sarcoid heart disease. Granulomatous lesions with no apparent transition forms between myofibres and giant cells. H & E, × 65.

Giant cell granulomas are of two types. In giant cell myocarditis (Fig. 3) the myogenic nature of the giant cells is clear. Various stages from abnormal myofibres to isolated multinucleate giant cells can usually be readily identified. The giant cells of sarcoid (Fig. 4) tuberculous or fungal myocarditis are larger, with no features suggesting a myofibre origin and may contain inclusions or micro-organisms which can be demonstrated by appropriate stains.

In the collagen diseases inflammation is associated with fibrinoid or basophilic degeneration of interstitial myocardial connective tissue which is usually best seen around small vessels.

Most examples of inflammatory myocardial disease are either infective or of unknown pathogenesis. Myocarditis has been reported with almost every known human pathogenic organism, and Table 2 makes no attempt at comprehensiveness.

In this country Coxsackie infections are comparatively common, and tuberculous infections are increasingly diagnosed, particularly in the elderly. Fungal infections are rare and occur mainly in patients already in hospital, either on immunosuppressive therapy or with conditions such as disseminated malignancy in which the body immunology is abnormal. Of the protozoal diseases, toxoplasma myocarditis is well recognized, and in South America, Chagas' disease is common. Helminthic infestation of the heart is rare and from my very limited experience of this pathological curiosity it seems that extensive myocardial involvement may be present without any clinical symptoms. Giant cell granulomatous reactions may be caused by mycobacteria or fungi but most cases are of unknown aetiology. There is a possibility that a transmissible agent has been identified in sarcoid, but similar attempts in giant cell myocarditis have so far been unsuccessful. Apart from the proven association between group A haemolytic streptococcal infection and rheumatic fever the pathogenesis of the collagen diseases is still obscure, although there is strong evidence suggesting that immunological factors are concerned in all.

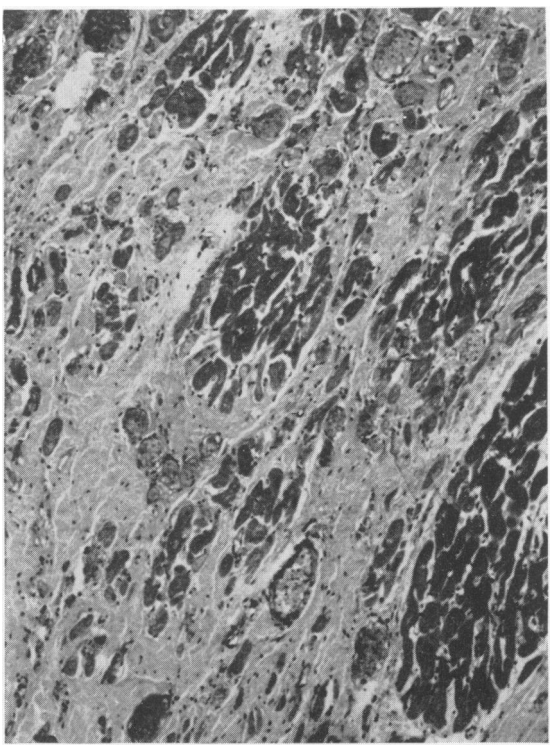

FIG. 5. Diffuse myocardial fibrosis. The fibrous tissue surrounds small groups and isolated myofibres. Many large bizarre nuclei are present. From a patient with muscular dystrophy. H & E, ×65.

Diseases associated with myocardial fibrosis

Histological changes vary from the fine interstitial strands of collagen which develop following myocarditis, to extensive replacement of myofibres by large areas of fibrous tissue, as in scleroderma. Marked variation in fibre size, vacuolation and bizarre large nuclei are not uncommon and have no diagnostic significance. In most cases the aetiology of the fibrosis is no longer apparent. Pathologists generally assume such cases are due to previous myocarditis, although some classify them as primary cardiomyopathies when no clinical evidence of an acute illness is obtained. Less common causes of non-coronary myocardial fibrosis are the genetic neuromuscular diseases, in particular Freidreich's ataxia and the muscular dystrophies (Fig. 5) and the collagen diseases. Marked myocardial fibrosis is common in scleroderma, and rheumatic carditis may also be followed by quite extensive myocardial fibrosis. Rarely mucoviscidosis is associated with extensive myocardial fibrosis, which has been attributed to vitamin deficiencies from malabsorption. Iatrogenic fibrosis is an occasional sequel of cardiac surgery and may also follow radiotherapy for carcinoma of breast or lung if the patient survives long enough. Cardiac fibrosis has also been attributed to methysergide, but cases reported so far have mainly involved the base of the heart or valves.

Abnormal depositions and infiltrations

The abnormality may be in the myofibres or in interstitial tissues. In glycogen storage disease the myofibres are grossly distorted, producing a characteristic lace-like pattern on histology (Fig. 6).

Accumulations of inorganic substances produce no significant distortion of the myofibres in most cases (Fig. 7). Cysts may form in severe haemochromatosis or haemosiderosis, and in dystrophic calcification the calcium often appears encrusted on the surface of the fibres.

Abnormal deposition between myofibres may be within histiocytes, as in mucopolysaccharidosis (Fig. 8) or extracellular, as in amyloidosis (Figs. 9 and 10) and myxoedema.

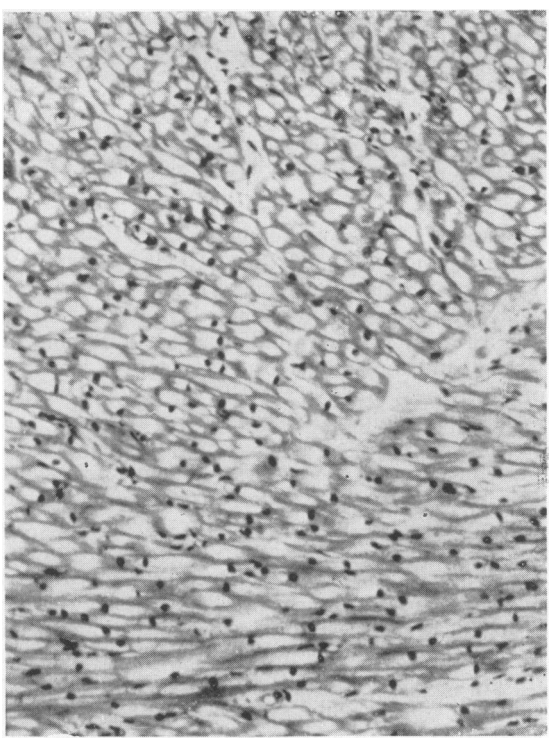

FIG. 6. Glycogen storage disease. All myofibres are distended by glycogen, resulting in a characteristic lace-like appearance. From a child dying, aged 8 months, with hemiplegia, congestive cardiac failure and bronchopneumonia. H & E, ×65.

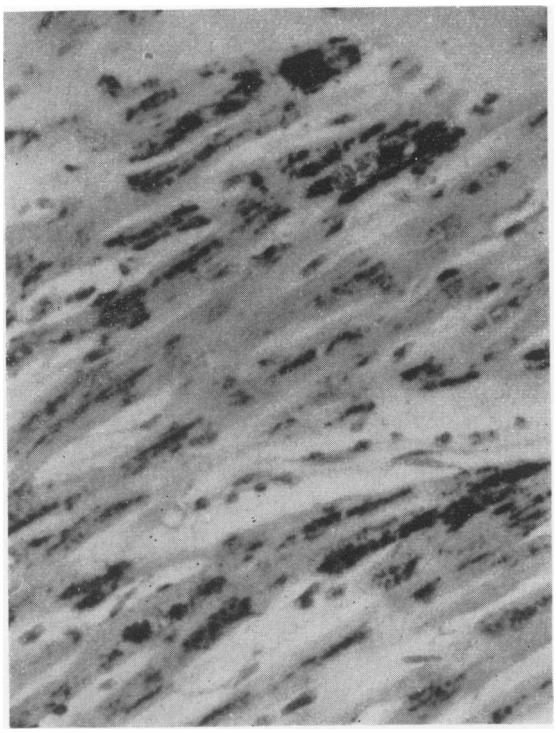

FIG. 7. Haemochromatosis. Granular pigment in muscle fibres which retain their normal size and shape. Perl's stain, ×290.

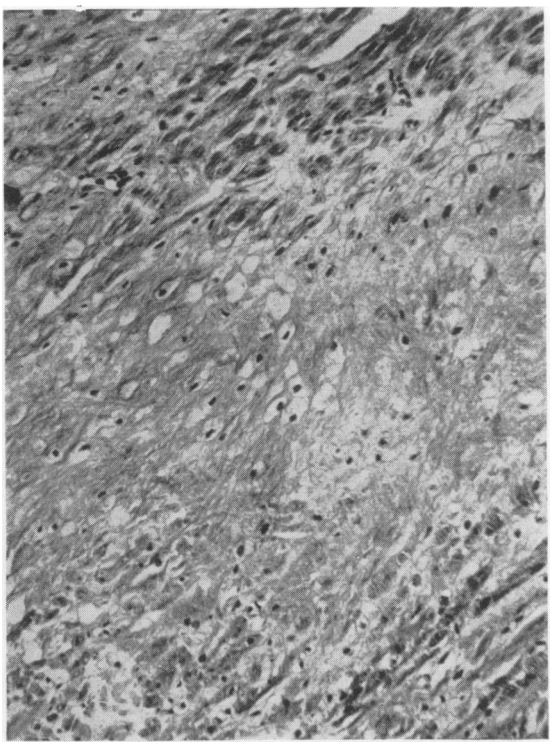

FIG. 8. Mucopolysaccharidosis. An area of myocardial fibrosis containing numerous large 'clear cells', which are histiocytes distended by mucopolysaccharide. From an 11-year-old-girl with gargoylism. H & E ×65.

Amyloidosis is the only common condition in this category and cases fall into two distinct groups. The most familiar type is the classical primary type which occurs mainly in patients between 45 and 70 years and in which cardiomegaly is a prominent feature and amyloid is usually plentiful in other organs. The other type, senile cardiac amyloid, is much more common, being found in about 10% of patients over 70 years old; it also may be responsible for cardiac failure. These patients are usually seen by the general practitioner or geriatrician and are rarely seen in specialized cardiac units. In contrast to the classical primary type the amyloid is, for all practical purposes, confined to the heart, and does not cause cardiomegaly. The pathology of the heart differs slightly in these two forms, compression atrophy of surrounded myofibres being a prominent feature of the senile cardiac type (Fig. 9), while in the classical type myofibres are widely separated by amyloid (Fig. 10) and atrophy is not conspicuous until a very late stage. Amyloid thus tends simply to replace myofibres in the senile type and no increase in weight occurs, while in primary amyloidosis it adds to the substance of the heart and weights of up to 1000 g are not uncommon.

Many of the conditions in this group are genetically determined. In glycogen and lipid storage diseases, mucopolysaccharidoses and oxalosis, enzyme deficiencies are present while in haemochromatosis the deficiency is in the gastric substance controlling iron absorption. Calcium deposition results from either generalized or localized metabolic abnormalities and can occur in any condition in which the serum calcium is high, as well as in localized areas of degenerate myocardium from any cause. The aetiology of amyloidosis is obscure. It is known to be associated with ageing in many animals including man. Some cases are undoubtedly familial and it has been suggested that isolated cases of primary amyloidosis are simply sporadic cases of a genetically determined form.

Small vessel disease

This may not be suspected on gross examination, but cardiac failure from multiple small coronary emboli is not uncommon in infective endocarditis (Fig. 11). Emboli have been reported in up to 66% of cases of non-bacterial endocarditis, though this

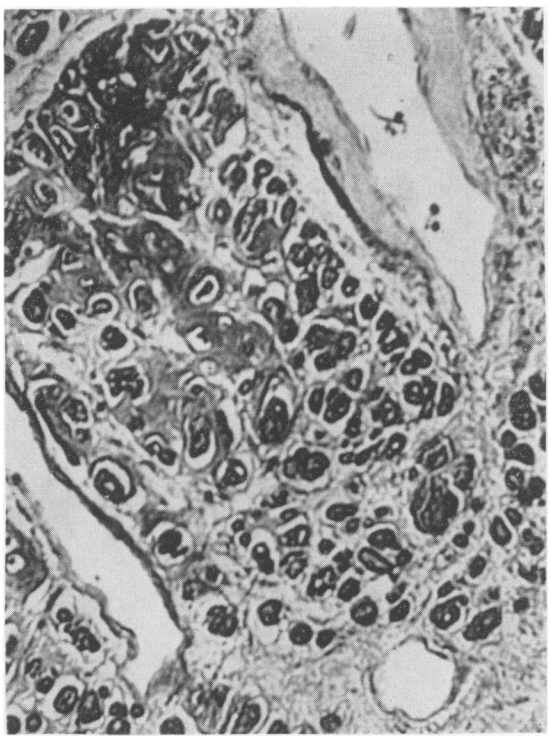

FIG. 9. Senile cardiac amyloidoisis, showing compression and atrophy of myofibres and replacement by amyloid deposits. No amyloid is present in the vessels. From a man of 82. Crystal violet, ×80.

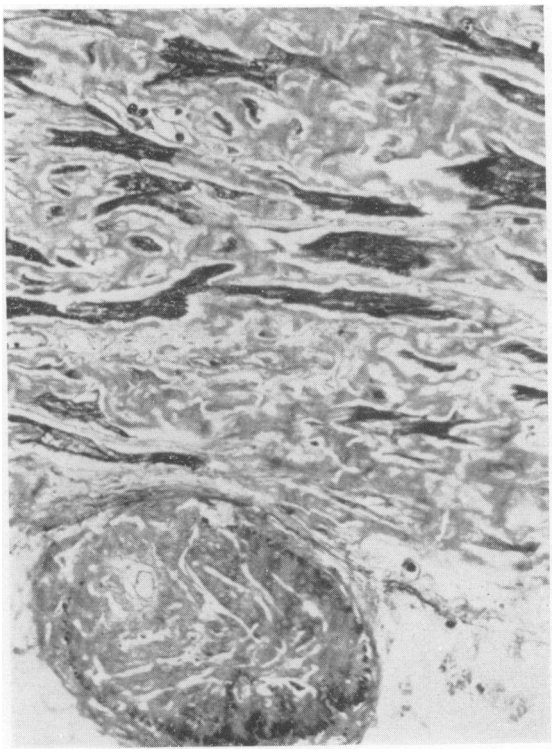

FIG. 10. Cardiac amyloid in a man aged 66. Myofibres are widely separated by amyloid deposits. The heart weighed 950 g. Crystal violet, ×95.

is rarely of clinical importance since most of these patients have died with disseminated malignant disease. Inflammatory small vessel (Fig. 12) disease is usually found in the collagen diseases group, in particular polyarteritis nodosa and Wegener's granulomatosis. It is characterized by necrosis and dense inflammatory cell infiltration of the walls of small arteries. Non-inflammatory focal degeneration of small coronary arteries has also been described (James, 1967).

Non-specific changes and conditions with no apparent changes

In many conditions known to be associated with cardiac failure routine sections show either no apparent abnormality or only minor non-specific changes such as a minor degree of fatty change in myofibres, focal myofibre necrosis, and scanty small aggregates of polymorphs. These findings are non-specific and are not infrequently observed in patients dying of non-cardiac conditions. Specialized histochemistry and electron microscopy may show changes where no abnormality is apparent on routine H & E stained material, but such techniques are not practicable in most hospital pathology departments. The nutritional, toxic and endocrine causes of heart disease all come into this group. Nutritional heart disease includes vitamin and possibly protein deficiencies and the anaemias. Chemicals known to be responsible for heart disease include emetine, antimony and cobalt, which is sometimes a constituent of beer. Alcohol must be included as a toxin, although nutritional factors may also be involved in alcoholic heart disease. The phenothiazine group of tranquillizers have recently come under suspicion as a cause of myocardial abnormalities and sudden death. Amongst endocrine causes of cardiac failure thyrotoxicosis is the most common, particularly in elderly patients, but cardiomegaly and failure are well recognized features of myxoedema, acromegaly and Cushing's disease. Finally, specific pathology is also absent in heart disease secondary to chronic lung disease or to vascular shunts, and although these conditions are not usually included as secondary cardiomyopathies, they must nevertheless be

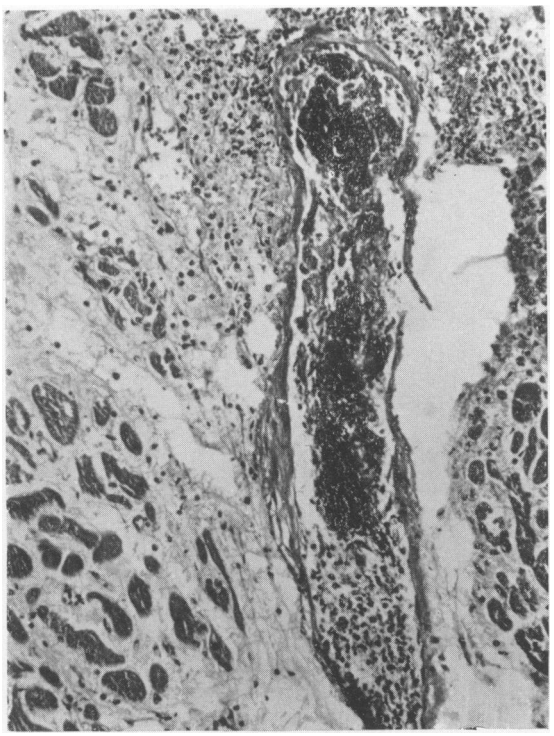

FIG. 11. Coronary microembolism in infective endocarditis. Fragments of bacterial vegetation occlude a small artery. H & E, × 150.

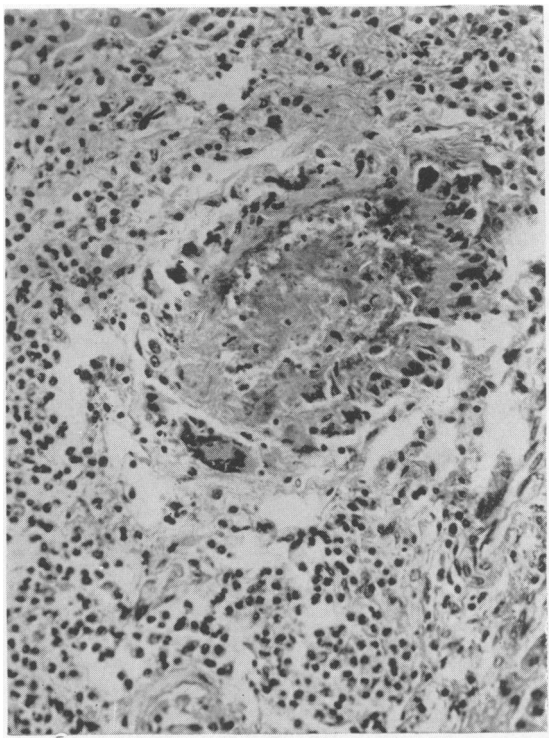

FIG. 12. Inflammatory small vessel disease. A small coronary artery shows necrosis and inflammatory cell infiltration of the wall, with giant cells, and the lumen is occluded by thrombus. From a patient with Wegener's granulomatosis. H & E, × 115.

excluded before a diagnosis of primary cardiomyopathy can be made.

This classification of secondary cardiomyopathies differs in presentation from the usual list found in papers on cardiomyopathies, although the conditions included are the same. The known causes or associations of heart muscle disease have been grouped according to the pathological findings since this is the view seen by the pathologist.

Acknowledgments

Thanks are due to the friends and colleagues who provided material for many of the illustrations—Dr J. W. Lacey for Coxsackie myocarditis, sarcoidosis and muscular dystrophy, Dr M. Bennett for glycogen storage disease, and Dr J. Bradley-Watson for chronic myocarditis and cardiac amyloidosis. I am also grateful to Dr M. J. Davies for Figs. 1 and 3.

Figs. 1 and 3–10 inclusive are from *Pomerance and Davies, Pathology of the Heart*, 1972, and are reproduced by permission of Blackwell's Scientific Publications Ltd.

Bibliography

General reviews or classifications of cardiomyopathies

EMANUEL, R. (1970) A classification for the cardiomyopathies. *American Journal of Cardiology*, **26,** 438.

FOWLER, N.O. (1971) Differential diagnosis of cardiomyopathies. *Progress in Cardiovascular Diseases*, **14,** 113.

HUDSON, R.E.B. (1970) The cardiomyopathies: order from chaos. *American Journal of Cardiology*, **25,** 70.

PERLOFF, J.K. (1971). The cardiomyopathies—current perspectives. *Circulation*, **44,** 942.

PERLOFF, J.K., LINDGREN, K.M. & GROVES, B.M. (1970) Uncommon or commonly unrecognized causes of heart failure. *Progress in Cardiovascular Diseases*, **12,** 409.

Cardiac involvment in individual diseases

ABELMANN, W.H. (1966) Myocarditis. *New England Journal of Medicine*, **275,** 832.

ABELMANN, W.H. (1971) Virus and the heart. *Circulation*, **44,** 950.

ALEXANDER, C.S. (1968) The concept of alcoholic myocardiopathy. *Medical Clinics of North American*, **52,** 1183.

ARNASON, G., BERGE, T.H. & DAHLBERG, L. (1964) Myocardial changes in dystrophia myotonica. *Acta Medica Scandinavica*, **176,** 535

BARBORIK, M. & DUSEK, J. (1972) Cardiomyopathy accompanying industrial cobalt exposure. *British Heart Journal*, **34,** 113.

BASHOUR, F.A., MCCONNELL, T. SKINNER, W. & HANSON, M. (1968) Myocardial sarcoidosis. *Diseases of the Chest*, **53,** 413.

BRITISH MEDICAL JOURNAL (1971) Cardiovascular complications from psychotropic drugs. Leading article. **1,** 3.

BRIGDEN, W. (1964) Cardiac amyloidosis. *Progress in Cardiovascular Diseases*, **7,** 142.

BUERGER, L. & BRAUNSTEIN, H. (1960) Senile cardiac amyloidosis. *American Journal of Medicine*, **28**, 357.

BUJA, L.M. & ROBERTS, W.C. (1971) Iron in the heart. *American Journal of Medicine*, **51**, 209.

BUJA, L.M., KHOI, N.B. & ROBERTS, W.C. (1970) Clinically significant cardiac amyloidosis. Clinicopathologic findings in fifteen patients. *American Journal of Cardiology*, **26**, 394.

EHLERS, K.H., HAGSTROM, J.W.C., LUKAS, D.S., REDO, S.F. & ENGLE, M.A. (1962) Glycogen-storage disease of the myocardium with obstruction to left ventricular outflow. *Circulation*, **25**, 96.

FAJARDO, M.D., STEWART, J.R. & COHN, K.E. (1968) Morphology of radiation-induced heart disease. *Archives of Pathology*, **86**, 512.

GAFNI, J., SOHAR, E. & HELLER, H. (1964) The inherited amyloidoses: their clinical and theoretical significance. *Lancet*, **i**, 71.

GILROY, J., CAHALAN, J.L., BERMAN, R. & NEWMAN, M. (1963) Cardiac and pulmonary complications in Duchenne's progressive muscular dystrophy. *Circulation*, **27**, 484.

GORE, I. & KLINE, I.K. (1968) Myocarditis. In: *Pathology of the Heart* (Ed. by S.E. Gould), Chap. 14. Thomas, Springfield.

HEWER, R.L. (1969) The heart in Friedreich's ataxia. *British Heart Journal*, **31**, 5.

JAMES, T.N. (1967) Pathology of small coronary arteries. *American Journal of Cardiology*, **20**, 679.

KLEMPERER, P., POLLACK, A.D. & BAEHR, G. (1941) Pathology of disseminated lupus erythematosus. *Archives of Pathology*, **32**, 569.

KOTEN, J.W., VAN GASTEL, C., DORHOUTMEES, E.J., HOLLEMAN, L.W.J. & SCHUILING, R.D. (1965) Two cases of primary oxalosis. *Journal of Clinical Pathology*, **18**, 223.

MCKUSICK, V.A. (1966) *Heritable Disorders of Connective Tissue*, 3rd edn. C. V. Mosby, St Louis.

MOUY, A. & TORDJMANN, M. (1968) Myocardial fibrosis in the course of mucoviscidosis. *Archives françaises de pediatrie*, **25**, 687.

MULLER, O.F., BELLET, S. & ERTRUGRUL, A. (1961) Glycogen-storage disease. Report of a case with generalised glycogenosis and a review of the literature. *Circulation*, **23**, 264.

ORAM, S. & STOKES, W. (1961) The heart in scleroderma. *British Heart Journal*, **23**, 243.

PERLOFF, J.K. (1971) Cardiomyopathy associated with heredofamilial neuromyopathic diseases. *Modern Concepts of Cardiovascular Disease*, **40**, 23.

POMERANCE, A. (1966) The pathology of senile cardiac amyloidosis. *Journal of Pathology and Bacteriology*, **91**, 357.

PORTER, G. (1960) Sarcoid heart disease. *New England Journa of Medicine*, **263**, 1350.

PYUN, K.S., KIM, Y.H., KATZENSTEIN, R.E. & KIKKAWA, Y. (1970) Giant cell myocarditis. *Archives of Pathology*, **90**, 181.

SLAMA, R., JOSSO, F. & ANTOINE, B. (1960) Myocardial manifestations of oxalosis. *Archives des maladies du coeur et des vaisseaux*, **53**, 917.

SYMMERS, W.St.C. (1956) Primary amyloidosis: a review. *Journal of Clinical Pathology*, **9**, 187.

WHITEHEAD, R. (1965) Isolated myocarditis. *British Heart Journal*, **27**, 220.